Journal of Genetics and Genetic Engineering
Volume 3, Issue 2, 2019, PP 7-14
ISSN 2637-5370

Most Common Autosomal Dominant Disorders in Clinical Practice, a Review

Sami Azrak*

Department of Medical Genetics, School of Medicine, Al AndalusUniversity for Medical Sciences, Al Qadmus, Syria

***Corresponding Author:** Sami Azrak, Department of Medical Genetics, School of Medicine, Al Andalus, University for Medical Sciences, Al Qadmus, Syria, Email: s.azrak@au.edu.sy*

ABSTRACT

Autosomal dominant disorders occur when only one defective copy of an autosomal gene required to cause disease. As a result, affected individuals have one normal and one mutated allele. A parent with an autosomal dominant condition has a 50% chance of having a child with the condition. Therefore, disorders can be inherited from one affected parent who also has one defective copy of the gene, or can occur sporadically as a result of a new mutation in a patient with no family history. In is this review, we aimed to discuss clinical features, disease-related gene product, diagnosis and treatment of most common autosomal dominant disorders, such as Achodrplasia, Adult polycystic kidney disease, Charcot-Marie-Tooth, Familial Hypercholesterolaemia, Hereditary Haemorrhagic Telangiectasia, Marfan syndrome, Osteogenesis imperfecta, Otosclerosis, Porphyrias and Von Willebrand disease.

Keywords: *Achondroplasia, Otosclerosis, Marfan syndrome, Osteogenesisimperfecta, Von Willebrand disease.*

INTRODUCTION

Achondroplasia

Clinical Features

Achondroplasia is the most common of the human skeletal disorders, affecting 1/20.000 to 1/40.000 live births. Individuals manifest short stature (with adult high about 1.2m) short-ended limbs, exaggerated lumbar lordosis (swaybackness), and macrocephaly (enlarged head circumstances) with frontal bossing (prominence) (Daugherty 2017). Medical problems include reduce muscles tone (hypotonic) in almost all infants along with an increased risk for cessation of breathing (apnoea) due to brainstem compression or obstruction of the airways. The most common complications during adulthood are obesity and compression of the spinal cord or spinal nerves due to narrowing of the spinal canal (spinal stenosis) Intelligence is usually normal. Over 80% of cases have no family history of achondroplasia and are caused by a de novo mutation on the paternally inherited chromosome 4, often in association with advanced paternal age.

Genes and Disease-Related Gene Products

Achondroplasia is always cause by a mutation in the Fibroblast growth factor receptor 3 gene (FGFR3) (4p 16), which codes for a protein of the same name. Persons with achondroplasia are heterozygous for the FGFR3 mutation (Kylat .2017).If two persons with achondroplasia have children; their offspring have a 1 in 4 chance of being FGFR3 mutation homozygotes. These homozygotes produce a lethal short stature phenotype. The FGFR3protein is a tyrosine kinase receptor that binds ligands belonging to the fibroblast growth factor family. Normally, ligand binding activates the receptor and initiates signal cascades important for cell growth and differentiation. The mutation responsible for achondroplasia causes constitutive (i.e. ligand-independent) activation of the FGFR3 receptor. Several different mutations in FGFR3 result in skeletal dysplasias and the greater the extent of ligand-independent activation, the greater the severity of the dysplasia.

Diagnosis

The diagnosis is suggested by clinical findings and characteristic appearance on skeletal X-rays. Virtually all patients with achondroplasia

have a mutation in the same FGFR3 nucleotide (1138), suggesting this may be the most mutable nucleotide in the human genome. Mutation testing is clinically available.

Treatment

Current treatments include surgical correction of medical complications such as spinal stenosis. Options to maximize stature include growth hormone supplementation and/or surgical limb lengthening.

Adult Polycystic Kidney Disease

Clinical Features

The most common heritable renal disease, affecting 1/500-1/1000 persons, is an autosomal dominant condition in which renal failure results from progressive cystic degeneration of the kidneys. Cysts can also occur in other organs, including the liver; extra-renal anomalies such as vascular aneurysms, diverticular disease, hernias and cardiac valve abnormalities are more common in affected patients. Hypertension is often an early symptom (Lanktreeet al. 2018).

Gene and Disease-Related Gene Product

Approximately 85% of cases are due to a defect in PKD1 which maps to 16pl3.3 and encodes the protein polycystin1.The protein's exact functions remain unknown but it is a large membrane receptor, localized to renal epithelia cell cilia, that complex with multiple proteins. Most mutations result in loss of function of polycystin (Harriset al. 2018).

Diagnosis

The diagnosis is strongly suggested by the characteristic appearance of renal cysts on sonography. Cysts increase in number over time. Almost 100 different mutations have been identified each in PKD1 and PKD2. Commercially available testing is able to identify a mutation in 75% of patients with PKD1 and in an even higher percent of patients with PKD2 (Stayneret al. 2018). More than three-quarters of the PKD1 gene is duplicated elsewhere on chromosome 16, so that screening for mutations requires care to ensure that they arise in PKD1 rather than in the duplicated regions.

Treatment

Controlling high blood pressure can delay the progression of the disease and slow further kidney damage, utilizing angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) medications. Combining a low-sodium, low-fat diet that's moderate in protein and calorie content with not smoking, increasing exercise and reducing stress may help control high blood pressure. If the kidneys lose their ability to remove waste products and extra fluids from your blood, you'll eventually need either dialysis or a kidney transplant.

Charcot-Marie-Tooth, Types 1 and 2 (Hereditary Motor and Sensory Neuropathies, HMSN)

Clinical Features

Charcot-Marie-Tooth (CMT) disease, named for Drs Charcot, Marie and Tooth in 1886, refers to a group of neurologic disorders producing progressive muscle weakness and distal muscle atrophy, decreased deep tendon reflexes, distal loss of sensation and pescavus (high arched foot). CMT, types 1 and 2, are both autosomal dominant disorders and symptoms generally develop between childhood and 30 years of age (Anzaloneet al. 2018). There are numerous CMT subtypes, classified according to the speed of nerve conduction velocities, the mutant gene and the pattern of inheritance.CMT1A is the most common subtype of CMT and is caused by 1.5 Mbp duplication on chromosome 17p11. This results in duplication of the PMP22 gene those codes for peripheral myelin protein 22. Nerve conduction velocity is slowed, as CMT1A is a demyelinating disorder.

Ankle weakness with bilateral foot drop is very common, as an inverted 'champagne-bottle' appearance to the legs, due to lower leg muscle atrophy. Independent ambulation is generally maintained and life expectancy is normal (Azevedoetal2018). Meanwhile CMT1B has a similar phenotype to 1A but is caused by mutations in the gene MPZ that code for myelin protein zero.

CMT2 is clinically similar to the CMT1's, but generally has normal nerve conduction velocities and a milder phenotype. There are numerous CMT2 subtypes, and responsible mutations have been found in seven different genes. CMT1A is a 'micro duplication' disorder. Similar to the 'micro deletion' disorders discussed, homologous stretches of DNA, or duplicons, flank the region and predispose to abnormal alignment and unequal crossing over of the chromosome 17's during meiosis. The critical gene in this duplicated region is PMP22. An extra copy of PMP22 produces increased mRNA,

which damages peripheral nerve myelin ultimately leading to axonal degeneration, by an unknown mechanism

Diagnosis

Nerve conduction studies should be the initial laboratory test when considering the diagnosis of CMT. Duplication of the PMP22 gene responsible for CMT1A can be detected by FISH or Southern blotting; this testing is widely available (Cannarellaet al. 2018). Very rarely, CMT is due to a point mutation in PMP22; gene sequencing to detect such mutations is also commercially available. Mutation testing is available in some of the other genes that cause CMT, in either a commercial or research laboratory.

Treatment

The treatment in general is supportive. Since many CMT subtypes follow an autosomal dominant pattern of inheritance, clinical and genetic examination of the first degree relatives of an affected individual is indicated.

Familial Hypercholesterolaemia

Clinical Features

Familial hypercholesterolaemia is the most common single gene disorder affecting lipid metabolism. It is usually caused by a mutation in the gene LDLR coding for the low density lipoprotein receptor protein. Approximately 1/500 persons are familial hyper cholesterolaemia heterozygotes, carrying one mutant copy of the gene; these gene carriers have elevated low density lipoprotein (LDL) cholesterol levels with an increased risk for premature coronary artery disease.

About 1/million persons are Familial hyper cholesterolaemia homozygotes and have markedly elevated LDL levels and develop refractory atherosclerosis starting in childhood (Nairet al. 2014).

Diagnosis

Diagnosis is generally based on family history, cholesterol history, presence or absence of xanthomas and results of a fasting lipid profile. Total cholesterol levels between ~9 and 13 mmol/l and between -18 and 31 mmol/l are consistent with heterozygous and homozygous familial hypercholesterolemia, respectively; LDL cholesterol levels are the most significantly elevated. Since there are many different LDLR mutations, most unique to a given family, molecular methods are rarely used to establish the diagnosis in clinical practice (Sturm et al. 2018).

Treatment

Homozygotes respond poorly to standard treatments but do show improvement following liver transplantation (Sturm et al. 2018). Cholesterol levels can be lowered in heterozygotes by use of HMG CoA reductase inhibitors (so-called statins) and/or resins which prevent dietary cholesterol absorption from the gastrointestinal tract. Gene therapies, such as the introduction of a functioning LDLR gene, are currently being developed.

Hereditary Haemorrhagic Telangiectasia

Clinical Features

Hereditary Haemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a disorder of abnormal blood vessel formation whose features develop over time. The prevalence is estimated to be 1/10 000. Universal signs, present in all affected persons by age 40, are skin and mucosal telangiectasias (small arteriovenous malformations involving a direct connection between arteries and veins). Telangiectasias predispose to recurrent nosebleeds (usually present in childhood) and gastrointestinal bleeds (Rimmer and Lund. 2015). A substantial number of patients also suffer from large arteriovenous malformations, most commonly found in the lung, liver and brain. The lung vascular malformations can produce exercise intolerance and cyanosis due to abnormal admixture of arterial and venous circulations, but also can declare themselves by causing a pulmonary haemorrhage, a cerebral abscess or stroke.

Gene and Disease-Related Gene Product

Mutations in two genes cause HHT. Most cases of HHT are due to mutations in the gene endoglin (9q34.1). These mutations lead to production of an abnormally truncated protein product, so that the features of HHT are caused by insufficient amounts of endoglin protein, so-called protein haploinsufficiency "Protein Haplo insuffiency". The endoglin knockout mouse recapitulates the human phenotype. Endoglin is a membrane protein found on vascular endothelium, where it binds transforming growth factor-beta (TGF-β). It has been speculated that endoglin deficiency interferes with TGF-β'ssignalling on endothelial cells which, by an unknown mechanism, contributes to the blood vessel pathology of HHT. Mutations in a second gene, an activin A receptor, (ACVRL1, 12q11-

14) cause ~20% of HHT cases (Macri and Bermudez. 2018).

Diagnosis

Clinical diagnosis is established when three of the following findings are present: telangiectasias, recurrent nosebleeds, positive family history or arteriovenous malformations. Genetic testing to detect ENG and ACVRL1 mutations is clinically available (Gamboaet al. 2018). Mutations can be identified by sequencing the coding regions of the gene; quantitative PCR can supplement sequencing to detect deletions, rather than point mutations.

Treatment

Recurrent bleeds may require iron supplementation or even transfusions. The abnormal connection between a pulmonary artery and vein can be closed by transcatheter embolization, done in specialized centers (Gamboaet al. 2018). Knockout animal models of HHT may lead to a better understanding of the disease path physiology and eventually provide therapeutic insights.

Marfan syndrome

Clinical Features

Marfan syndrome is a disorder affecting ~1/5000 individuals. Common musculoskeletal abnormalities include relatively tall stature with disproportionately long limbs and digits (compared to non- affected family members), scoliosis (curvature of the spine) and deformities of the sternum (pectus). Involvement of the cardiovascular system can be relatively minor (mitral valve prolapse in which floppiness of the mitral valve in the heart prevents normal closure) or life-threatening (dilatation of the aortic root, aneurysms [a weakness in the wall of a blood vessel causing abnormal widening], and/or dissection [a tear leading to separation of the layers of a blood vessel]) (Ekhomu and Naheed. 2015).

Gene and Disease-Related Gene Product

The FBN1 gene (15q21.1) encodes fibrillin 1, a major protein component of microfibrils. Microfibrils determine the architecture of the extracellular matrix in connective tissue. A variety of missense and nonsense mutations in FBN1 produce the Marfan phenotype.

Fibrillin deficiency in a knockout Marfan mouse model leads to excessive activation of transform growth factor-beta (TGF-β). TGF-β, a polypeptide hormone that typically functions in immune protection, regulates the production of connective tissue protein and its excess could contribute to some of the physical findings of Marfan syndrome.

Diagnosis

The diagnosis of Marfan syndrome is based on clinical consensus criteria established by a panel of experts, rather than a laboratory test. Findings from detailed physical examination, family history, slit-lamp ophthalmologic examination and an echocardiogram are combined to decide whether or not a patient has Marfan syndrome. Even though several hundred different mutations in FBN1 have been identified, mutation screening is complicated and not routinely employed for diagnostic purposes. A fibrillin mutation is not always identified in persons clinically diagnosed with Marfan syndrome, and even among those in whom a mutation is found, it provides little prognostic information about the phenotype.

Treatment

Current therapies are directed at preventing or treating medical problems, such as use of a beta-blocker antihypertensive agent to slow the rate of aortic root dilatation, or surgical repair of an already dilated aortic root (Lindsay. 2018). Frequent medical monitoring should include formal ophthalmologic examinations, echo cardiography and scanning of major blood vessels to identify cardiovascular complications and treat them early in their course.

Osteogenesisimperfecta

Clinical Features

Osteogenesisimperfecta (OI) is a disorder of collagen, affecting 1/10 000-1/20 000 livebirths, and is referred to in lay terms as 'brittle bone' disease. The hallmark features of the disorder involve excess bone fragility associated with decreased bone density leading to frequent fractures and abnormal long bone contour (such as bowing of the femurs).

There can be additional connective tissue manifestations, all due to the underlying collagen defect, including blue discoloration of the sclerae, dentin genesis imperfect (discolored fragile teeth), and late onset hearing loss, short stature, scoliosis and joint laxity. The body contains numerous collagen moieties but most OI is caused by abnormalities in the most abundant collagen, type 1. Normally formed mature type 1 collagen is made of three chains, two coded for by the collagen 1A1 (COL1A1)

gene and one coded for by the collagen 1A2 (COL1A2) gene (Mariniet al. 2017). The three chains are able to form a tightly wound triple helix, in part because every third amino acid in the chain is a glycine, the smallest amino acid. OI results when a mutation leads either to the substitution of a bulky amino acid for one of the glycine residues, or when a decreased amount of structurally normal collagen is produced. Mutations that inactivate a function are usually recessive. Rarely non-functional mutations can be dominant if the mutant protein is expressed and interferes with the action of the normal protein by competing with it or in some way interfering with its normal role. Dominant-negative mutations can be created in the laboratory and can be used in research to identify protein function.

Diagnosis

The diagnosis of OI is suspected on clinical grounds and/or family history. Radiographic findings, such as osteopenia and Wormian bones (multiple bone islands seen on skull X-ray) are highly suggestive of the disorder. Definitive diagnosis can be established in ~90% of cases either by demonstrating a mutation in the Collagen 1A1 or 1A2 gene, or by documenting abnormal electrophoretic mobility of, or quantity of, the type 1 procollagen protein. Both of these tests are available in specialized clinical laboratories (Palomoet al. 2017).

Treatment

Current therapy involves avoidance of fractures and treatment of those that do occur. Recent studies show that bisphosphonates, most commonly used to treat osteoporosis in post menopausal women, increases bone density and decrease fractures in patients with OI

Otosclerosis

Clinical Features

Otosclerosis is the most common form of adult hearing loss. Hearing loss generally begins before the thirtieth birthday and progressively worsens at a slow pace. The disorder is autosomal dominant with incomplete penetrance. Abnormal growth of endochondral bone in the middle ear results in stapes fixation producing conductive hearing loss. In a minority of patients, the bone growth also extends into the inner ear compromising the VHIIIth cranial nerve, so that these patients have combined conductive and sensorineural hearing loss. Hearing loss is bilateral in most patients, especially in women (McElveenet al. 2018).

Genes and Disease-Related Gene Products

The genes responsible for otosclerosis have not been identified to date. However, linkage analysis applied to autosomal dominant kindreds with multiple affected family members has identified at least three different chromosomal loci (Chromosomes 15q25-26, 7q34-36 and 6p22.3-21.3). Thus, otosclerosis demonstrates considerable genetic heterogeneity, as mutations in at least three different genes result in the phenotype.

Diagnosis

Otosclerosis is diagnosed by health care providers who specialize in hearing. These include an otolaryngologist (commonly called an ENT because they are doctors who specialize in diseases of the ears, nose, throat, and neck), an otologist (a doctor who specializes in diseases of the ears), or an audiologist (a health care professional trained to identify, measure, and treat hearing disorders) (Ramaswamy and Lustig.2017). The first step in a diagnosis is to rule out other diseases or health problems that can cause the same symptoms as Otosclerosis. Next steps include hearing tests that measure hearing sensitivity (audiogram) and middle-ear sound conduction (tympanogram). Sometimes, imaging tests, such as a CT scan are also used to diagnose otosclerosis.

Treatment

Surgical operations are widely performed, and it is a relatively simple procedure. Either the part of the stapes with the abnormal bone growth is removed in order to insert a tiny implant (stapedotomy), or the entire stapes bone is replaced by a small prosthesis (stapedectomy). Both surgeries can restore hearing. In many of the cases the symptoms of vertigo and tinnitus will also disappear.

Porphyrias

Clinical Features

The porphyrias are a group of several distinct disorders, sharing in common a defect in the synthesis of the oxygen-binding haeme component of haemoglobin. They are a rare example of a dominantly inherited metabolic disorder. King George III likely had porphyria and it has been suggested that Vincent van Gogh suffered from one of the porphyrias as well. The word derives from the Greek 'porphyr' meaning

purple and, as will be explained below, some patients have port-wine discolouration of their urine during acute attacks. Selected porphyrias are presented below since a complete discussion is beyond the scope of this text. Porphyrins (consisting of four pyrrole rings) are intermediates in haeme synthesis, a multi-step process controlled by several different enzymes (Besuret al. 2015). Symptoms, or attacks, of porphyria develop when an enzyme deficiency leads to the accumulation of haeme precursors, either predominantly in the liver (so-called hepatic porphyrias) or in the blood cells (erythropoietic porphyrias). Another classification scheme divides the porphyrias into whether neurological symptoms (acute porphyrias) or skin manifestations (cutaneous porphyrias) predominate. Symptoms of acute porphyrias typically develop after puberty and consist of bouts of severe abdominal pain and vomiting, muscle weakness and even paralysis, cranial nerve palsies, constipation due to ileus (lack of intestinal motility), hypertension and fluctuating psychiatric disturbance (including apathy, agitation and psychosis).

Genes and Disease-Related Gene Products

The most accurate method of classifying the porphyrias is according to their gene mutation and/or resulting enzyme deficiency. The most common porphyria, Acute Intermittent Porphyria (AIP), caused by mutations in the porphobilinogen deaminase (PBGD) gene (11q23.3), results in ~50% deficiency of the enzyme porphobilinogen deaminase in the haeme synthetic pathway (Karimet al.2015).

Diagnosis

Most of the porphyrias are autosomal dominant disorders caused by partial deficiencies of the enzyme in the pathway for haeme synthesis. Since genetic conditions due to enzyme deficiencies are usually autosomal recessive disorders, the porphyrias seem to be striking exception and it is likely that complete absence of haem biosynthetic enzyme would be incompatible with life. Given the intermittent and protean nature of symptoms, the porphyrias are difficult to diagnose. During a porphyria attack, massive amount of haem precursors accumulate and these are responsible for the symptoms of the disorders.

Treatment

Non-specific treatment of acute attacks includes removal of any inciting agents, hydration, glucose, pain control and management of electrolyte or neurological problems. Specific treatments aim to suppress haeme synthesis by inhibiting the first enzyme, ALA, in the pathway.

Erythropoietic protoporphyria is treated by avoidance of sun exposure and close monitoring to detect those at risk for liver damage. Liver accumulation of protoporphyrin can be reduced by administration of a cholic acid but once liver damage occurs liver transplantation is the treatment of choice. Medications, other than estrogens, do not exacerbate symptoms in the cutaneous or non-acute porphyrias (Schulenburg -Brand et al. 2014)

Von Willebrand Disease

Clinical Features

Von Willebrand disease is the most common inherited bleeding disorder.The most common symptoms are easy bruising, recurrent nosebleeds, and menorrhagia (excessive bleeding with menstrual periods). However, disease severity can vary among affected family members and even in the same individual over time (Castamanet al. 2013). Most patients have von Willebrand disease, type I, due to decreased amounts of von Willebrand factor, accompanied by decreased levels of Factor VIII.

Gene and Disease-Related Gene Product

Von Willebrand disease is caused by mutations in VWF (12p13.3). This gene codes for Von Willebrand factor, which is exclusively produced by endothelial cells and megakaryocytes, Von Willebrand factor plays a role in two aspects of normal haemo-stasis: (a) it allows platelets to attach to damaged areas of arterial vessels to initiate formation of a platelet plug; and (b) it stabilizes Factor VIII by covalently complexing with it. The latter function prevents degradation of Factor VIII making it available to participate in the coagulation cascade at the site of vascular damage. In the most common form of the disease, Von Willebrand type I, symptoms are generally mild and are due to decreased amounts of structurally normal Von Willebrand factor (as well as decreased Factor VIII level); both are generally reduced to 5-30% of normal(Roberts and Flood. 2015).

Diagnosis

Widely available tests of coagulation that assess function of clotting factors, such as prothrombin time (PT) and activated partial-thromboplastin

time (PTT), can be normal in Von Willebrand disease and are, therefore, not of diagnostic value. The specific laboratory test known as 'bleeding time' is always prolonged in Von Willebrand disease (as opposed to Haemophilia A where it is normal).

Treatment

Medications, such as aspirin and ibuprofen, which have anti-platelet effect, should not be taken by persons with Von Willebrand disease (Chapin. 2018). Standard treatments for those with clinically significant bleeding problems include DDAVP (desmopressin inhaled as a nasal spray) which results in rapid increase in Factor VIII and Von Willebrand factor levels, Factor VIII concentrates (which normally also contain Von Willebrand factor) and anti fibrinolytic agents.

CONCLUSIONS

Autosomal dominant inheritance refers to the inheritance of a dominant gene mutation on an autosome (one of the chromosomes numbered 1-22). There are two copies of every autosomal gene. Both copies of the gene send a message to the cells to produce a particular product such as a protein. Individuals, who have a dominant mutation on one gene, and a working copy of that gene on the other partner chromosome, will be affected by that condition despite the working copy.

Therefore although one of the gene copies is correctly sending the instructions to make the gene product, the other copy with the dominant mutation is not sending the correct message and overrides the action of the working gene. A number of conditions follow this pattern of inheritance in families. While some are obvious at birth, in other cases the symptoms do not appear until much later in life.

REFERENCES

[1] Daugherty A. Achondroplasia: Etiology, Clinical Presentation, and Management. Neonatal Netw. 2017 Nov 1; 36(6):337-342. doi: 10.1891/0730-0832.36.6.337.

[2] Kylat RI. Achondroplasia and Biliary Atresia: A Rare Association and Review of Literature. J Pediatr Genet. 2017 Jun; 6(2):122-125.doi: 10. 1055/s-0036-1597930. Epub 2017 Jan 2.

[3] Lanktree MB, Iliuta IA, Haghighi A, Song X, Pei Y. Evolving role of genetic testing for the clinical management of autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2018 Aug 27. doi: 10.1093/ndt/gfy261.

[4] Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. Gene Reviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.

[5] Stayner C(1),Brooke DG, Bates M, Eccles MR. Targeted Therapies for Autosomal Dominant Polycystic Kidney Disease. Curr Med Chem. 2018May7doi:10.2174/0929867325666180508095654.

[6] Anzalone CL, Nuhanovic S, Olund AP, Carlson ML. Cochlear Implantation in Charcot-Marie-Tooth Disease: Case Report and Review of the Literature. Case Rep Med. 2018 Mar 26; 2018:1760978.doi:10.1155/2018/1760978. eCollection, 2018.

[7] Azevedo H, Pupe C, Pereira R, Nascimento OJM. Pain in Charcot-Marie-Tooth disease: an update.ArqNeuropsiquiatr.2018Apr; 76(4):273-276. doi: 10.1590/0004-282x20180021.

[8] Cannarella R, Burgio G, Vicari ES, La Vignera S, Condorelli RA, Calogero AE. Urogenital dysfunction in male patients with Charcot-Marie-Tooth: a systematic review. Aging Male. 2018 Jul 31:1-5.doi:10.1080/13685538.2018.1491543.

[9] Nair DR, Sharifi M, Al-Rasadi K. Familial hyper cholesterolaemia. urr Opin Cardiol. 2014 Jul; 29 (4):381-8.doi: 10.1097 /HCO.000000 00 00000083.

[10] Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, Ballantyne CM, Baum SJ, Bourbon M, Carrié A, Cuchel M, de Ferranti SD, Defesche JC, Freiberger T, Hershberger RE, Hovingh GK, Karayan L, Kastelein JJP, Kindt I, Lane SR, Leigh SE, Linton MF, Mata P, Neal WA, Nordestgaard BG, Santos RD, Harada-Shiba M, Sijbrands EJ, Stitziel NO, Yamashita S, Wilemon KA, Ledbetter DH, Rader DJ; Convened by the Familial Hypercholesterolemia Foundation. Clinical Genetic Testing for Familial Hyper cholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018 Aug 7; 72(6):662-680. doi: 10.1016/j.jacc.2018. 05.044.

[11] Rimmer J, Lund VJ. Hereditary haemorrhagic telangiectasia. Rhinology. 2015 Sep; 53(3):195-203.

[12] Macri A, Bermudez R. Osler-Weber-Rendu Disease (Hereditary Hemorrhagic Telangiectasia HHT). StatPearls. Treasure Island (FL): Stat Pearls Publishing; 2018 Feb 10.

[13] Gamboa NT, Joyce EJ, Eli I, Park MS, Taussky P, Schmidt RH, McDonald J, Whitehead KJ, Kalani MYS. Clinical presentation and treatment paradigms of brain arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. J Clin Neurosci. 2018 May; 51:22-28. doi: 10.1016/j.jocn.2018. 01.019. Epub 2018 Feb 23.

[14] Ekhomu O, Naheed ZJ. Aortic Involvement in Pediatric Marfan syndrome: A Review. Pediatr Cardiol.2015 Jun; 36(5):887-95. doi: 10. 1007/ s00246-015-1101-0. Epub 2015 Feb 11.

[15] Lindsay ME. Medical management of aortic disease in children with Marfan syndrome. Curr Opin Pediatr. 2018 Oct; 30(5):639-644.doi: 10.1097/MOP.0000000000000671.

[16] Marini JC, Forlino A, Bächinger HP, Bishop NJ, Byers PH, Paepe A, Fassier F, Fratzl-Zelman N, Kozloff KM, Krakow D, Montpetit K, Semler O. Osteo genesisimperfecta. Nat Rev Dis Primers. 2017 Aug 18; 3:17052. doi: 10 .1038 /nrdp.2017.52.

[17] Palomo T (1), Vilaça T, Lazaretti-Castro M. Osteogenesisimperfecta: diagnosis and treatment Curr Opin Endocrinol Diabetes Obes. 2017 Dec; 24(6): 381-388. doi: 10.1097/MED.0000 00000000 0367.

[18] McElveen JT Jr, Kutz JW Jr. Controversies in the Evaluation and Management of Otosclerosis. Otolaryngol Clin North Am. 2018 Apr; 51(2):487-499. doi:10.1016/j.otc.2017. 11.017.

[19] Ramaswamy AT, Lustig LR. Revision Surgery for Otosclerosis. OtolaryngolClin North Am. 2018 Apr; 51(2):463-474. doi: 10.1016/j.otc. 2017.11.014.

[20] Besur S, Schmeltzer P, Bonkovsky HL. Acute Porphyrias. J Emerg Med. 2015 Sep; 49(3): 305-12. doi: 10.1016/j.jemermed.2015. 04.034. Epub 2015 Jul 7.

[21] Karim Z, Lyoumi S, Nicolas G, Deybach JC, Gouya L, Puy H. Porphyrias: A 2015 update. Clin Res Hepatol Gastroenterol. 2015 Sep; 39(4):412-25. doi:10.1016/j.clinre.2015.05.009. Epub2015Jul 2.

[22] Schulenburg-Brand D, Katugampola R, Anstey AV, Badminton MN. The cutaneous porphyrias. DermatolClin. 2014 Jul; 32(3):369-84, ix. doi: 10.1016/j.det.2014.03.001.Epub 2014 May 5.

[23] Castaman G, Goodeve A, Eikenboom J; European Group on von Willebrand Disease. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica. 2013 May; 98(5):667-74. doi: 10.3324/haematol.2012.077263.

[24] Roberts JC, Flood VH. Laboratory diagnosis of von Willebrand disease. Int J Lab Hematol. 2015 May; 37Suppl 1:11-7. doi: 10.1111/ijlh .12345.

[25] Chapin J. Von Willebrand disease in the elderly: clinical perspectives. ClinInterv Aging. 2018 Aug 31; 13:1531-1541. doi: 10.2147/ CIA.S136931.

Citation: *Sami Azrak, "Most Common Autosomal Dominant Disorders in Clinical Practice, a Review", Journal of Genetics and Genetic Engineering, 3(2), 2019, pp, 7-14*